Is fall prevention by vitamin D mediated by a change in postural or dynamic balance?

Bischoff-Ferrari, H A ; Conzelmann, M ; Stähelin, H B ; Dick, W ; Carpenter, M G ; Adkin, A L ; Theiler, R ; Pfeifer, M ; Allum, J H J

Abstract: Introduction: The objectives were:(1) to validate a quantitative balance assessment method for fall risk prediction; (2) to investigate whether the effect of vitamin D and calcium on the risk of falling is mediated through postural or dynamic balance, as assessed by this method. Materials and methods: A secondary analysis of a double blind randomized controlled trial was employed, which included 64 institutionalized elderly women with complete balance assessment (age range: 65-97; mean 25-hydroxyvitamin D levels: 16.4ng/ml (SD ±9.9). Participants received 1,200mg calcium plus 800IU cholecalciferol (n=33) or 1,200mg calcium (n=31) per day over a 3-month treatment period. Using an electronic device attached to the lower back of the participant, balance was assessed as the degree of trunk angular displacement and angular velocity during a postural task (standing on two legs, eyes open, for 20 s) and a dynamic task (get up from a standard height chair with arm rests, sit down and then stand up again and remain standing). Results: It was found that both postural and dynamic balance independently and significantly predicted the rate of falling within the 3-month follow-up. Vitamin D plus calcium reduced the rate of falls by 60% [relative risk (RR)=0.40; 95% CI: 0.17, 0.94] if compared with calcium alone. Once postural and dynamic balance were added to the regression analysis, they both attenuated the effect of vitamin D plus calcium on the rate of falls. For postural balance, the RR changed by 22% from 0.40 to 0.62 if angular displacement was added to the model, and by 9% from 0.40 to 0.49 if angular velocity was added. For dynamic balance, it changed by 1% from 0.40 to 0.41 if angular displacement was added, and by 14% from 0.40 to 0.54 if angular velocity was added. Discussion: Thus, balance assessment using trunk angular displacement is a valid method for the prediction of falls in older women. Of the observed 60% reduction in the rate of falls by vitamin D plus calcium supplementation compared with calcium alone, up to 22% of the treatment effect was explained by a change in postural balance and up to 14% by dynamic balance

DOI: https://doi.org/10.1007/s00198-005-0030-9

Originally published at:
Bischoff-Ferrari, H A; Conzelmann, M; Stähelin, H B; Dick, W; Carpenter, M G; Adkin, A L; Theiler, R; Pfeifer, M; Allum, J H J (2006). Is fall prevention by vitamin D mediated by a change in postural or dynamic balance? Osteoporosis International, 17(5):656-663.
DOI: https://doi.org/10.1007/s00198-005-0030-9

Osteoporos Int (2006) 17: 656–663
DOI 10.1007/s00198-005-0030-9

ORIGINAL ARTICLE

Is fall prevention by vitamin D mediated by a change in postural or dynamic balance?

H. A. Bischoff-Ferrari · M. Conzelmann · H. B. Stähelin · W. Dick · M. G. Carpenter · A. L. Adkin · R. Theiler · M. Pfeifer · J. H. J. Allum

Received: 23 August 2005 / Accepted: 12 October 2005 / Published online: 1 March 2006

Abstract *Introduction:* The objectives were:(1) to validate a quantitative balance assessment method for fall risk prediction; (2) to investigate whether the effect of vitamin D and calcium on the risk of falling is mediated through postural or dynamic balance, as assessed by this method. *Materials and methods:* A secondary analysis of a double blind randomized controlled trial was employed, which included 64 institutionalized elderly women with complete balance assessment (age range: 65–97; mean 25–hydroxyvitamin D levels: 16.4 ng/ml (SD ±9.9). Participants received 1,200 mg calcium plus 800 IU cholecalciferol (*n*=33) or 1,200 mg calcium (*n*=31) per day over a 3-month treatment period. Using an electronic device attached to the lower back of the participant, balance was assessed as the degree of trunk angular displacement and angular velocity during a postural task (standing on two legs, eyes open, for 20 s) and a dynamic task (get up from a standard height chair with arm rests, sit down and then stand up again and remain standing). *Results:* It was found that both postural and dynamic balance independently and significantly predicted the rate of falling within the 3-month follow-up. Vitamin D plus calcium reduced the rate of falls by 60% [relative risk (RR)=0.40; 95% CI: 0.17, 0.94] if compared with calcium alone. Once postural and dynamic balance were added to the regression analysis, they both attenuated the effect of vitamin D plus calcium on the rate of falls. For postural balance, the RR changed by 22% from 0.40 to 0.62 if angular displacement was added to the model, and by 9% from 0.40 to 0.49 if angular velocity was added. For dynamic balance, it changed by 1% from 0.40 to 0.41 if angular displacement was added, and by 14% from 0.40 to 0.54 if angular velocity was added. *Discussion:* Thus, balance assessment using trunk angular displacement is a valid method for the prediction of falls in older women. Of the observed 60% reduction in the rate of falls by vitamin D plus calcium supplementation compared with calcium alone, up to 22% of the treatment effect was explained by a change in postural balance and up to 14% by dynamic balance.

Keywords Balance · Elderly · Fall prevention · Vitamin D

H. A. Bischoff-Ferrari (✉)
Department of Rheumatology
and Institute of Physical Medicine,
University Hospital Zurich,
Gloriastrasse 25,
8091 Zurich, Switzerland
e-mail: Heike.Bischoff@usz.ch
Fax: +1-617-7319032

H. A. Bischoff-Ferrari
Division of Rheumatology, Immunology and Allergy,
The Robert B. Brigham Arthritis and Musculoskeletal Clinical
Research Center, Brigham and Women's Hospital,
75 Francis Street,
Boston, MA 02115, USA

H. A. Bischoff-Ferrari · W. Dick
Department of Orthopedic Surgery,
University Basel,
Basel, Switzerland

M. Conzelmann
Department of Geriatrics, Felix Platter Spital,
Basel, Switzerland

H. B. Stähelin
Department of Geriatrics, University of Basel,
Basel, Switzerland

M. G. Carpenter · A. L. Adkin · J. H. J. Allum
Department of ORL, University Hospital,
Basel, Switzerland

M. G. Carpenter
Department of Neuroscience, Karolinska Institute,
Stockholm, Sweden

A. L. Adkin
Department of Physical Education and Kinesiology,
Brock University,
St Catherines, Canada

R. Theiler
Department of Rheumatology, Triemli StadtSpital,
Zurich, Switzerland

M. Pfeifer
Institute for Clinical Osteology,
Bad Pyrmont, Germany

Introduction

Falls are common in older people, leading to disability and loss of independence [1, 2]. At least 30% of all ambulatory elderly and 50% of all institutionalized elderly aged 65 report a fall once a year, and fall rates increase 10% per decade [3]. Serious injuries occur with 10–15% of falls and 5% lead to fractures [2, 4].

A recent meta-analysis of five randomized controlled trials (RCT) found that vitamin D should prevent more than 20% of falls in older persons [5]. The number needed to treat (NNT) was 15, or equivalently 15 subjects would need to be treated with vitamin D to prevent one person from falling. One of the mechanisms discussed is a direct effect of vitamin D on neuromuscular function [6–9] and balance [10], consequently leading to a decreased risk of falling. One trial found a significant 9% improvement of body-sway over a 2-month intervention with vitamin D plus calcium compared with calcium alone [10]. However, whether balance is the primary mediator of the vitamin D effect on falls has not been carefully examined. Alternatively, vitamin D may primarily affect muscle strength [7], which may translate into an improvement in lower extremity function [7, 11], better reaction time, and a reduction in the risk of falling [5].

The aims of this study were: first, to assess the validity of a new balance assessment method by examining whether postural and dynamic balance measures predict eventual rate of falls; second, to examine whether the treatment effect of vitamin D and calcium on the rate of falls is mediated by a change in postural or dynamic balance.

Materials and methods

Study population

From a population of 130 eligible elderly institutionalized women in two hospitals with long-stay geriatric care units (Geriatric University Hospital and Felix Platter Spital, Basel, Switzerland), 124 agreed to participate in the study. Of these 124 women, 122 were still hospitalized at the time of randomization and 89 subjects completed the study at 12-week follow-up. Of 89 subjects who completed the study, 25 had missing balance assessment at base-line or follow-up (11 subjects refused to join the measurements, four reported pain during measurements and ten had decreased compliance). Thus 64 subjects had complete balance assessment and were included in this secondary analysis of the original study [7]. Of these 64 women, 33 were in the vitamin D plus calcium group and 31 were in the calcium alone group.

Participants selected based on complete balance assessment did not differ significantly from the rest of the study population in regard to age, baseline 25-hydroxyvitamin D levels, baseline intact parathyroid hormone (iPTH) levels, baseline body mass index (BMI) and number of falls during a 2-week observation period before randomization [7]. Thus, the sub-sample of participants who entered this analysis are likely to be representative of the initial sample.

The study was carried out during the winter months (November 1999 and March 2000) in an attempt to accentuate as much as possible the differences in serum 25–hydroxyvitamin D concentrations between the treatment groups [7]. Fortification of food with vitamin D is not required in Switzerland. The study participants were frail elderly women in long-stay geriatric care, who were not able to live independently and were awaiting nursing home placement.

Eligibility criteria were age 60 or older and the ability to walk 3 m with or without a walking aid. Exclusion criteria were primary hyperparathyroidism, hypocalcemia, hypercalciuria, renal insufficiency (creatinine >117 µmol/l) and fracture or stroke within the last 3 months. Also excluded were those who had received any treatment with hormone replacement therapy, calcitonin, fluoride, or bisphosphonates during the previous 24 months. Previous vitamin D supplementation was not an exclusion criterion. None of the women were having physical training at study entry and no attempt was made to alter the subject's diet, strength or activity during the study. The study protocol was approved by the hospital ethics committee (University of Basel). Written informed consent was obtained from all subjects or from legal guardians.

Characteristics of the study population with complete balance measures are given in Table 1.

Study design and endpoints

The double-blind RCT had a 12–week treatment period. As in the original analysis, the rate of falls during the treatment period was the primary outcome. This outcome was chosen as subjects with recurrent falls are the frailest and have the highest risk for sustaining a fracture because of an increased exposure [12]. The secondary outcome of interest in the present analysis is change in postural and dynamic balance as potential mediators of the treatment effect of vitamin D plus calcium on the rate of falls.

Falls were recorded by the nurses on the inpatient units who had received training in the use of the fall protocol (date, time, circumstances, injuries). We used a standard fall definition, where falls are defined as "unintentionally coming to rest on the ground, floor, or other lower level" [13]. Coming to rest against furniture or a wall was not accounted as a fall [13]. Nurses completed the fall protocol if they observed or received a report of a fall.

Randomization was computer-based in blocks of four and performed by an independent statistician. Subjects randomly assigned to the vitamin D plus calcium group (vitamin D plus calcium group) received two tablets containing 600 mg of calcium carbonate and 400 IU of cholecalciferol per tablet (n=33). Subjects randomly assigned to the calcium group (calcium alone group) received two tablets containing 600 mg of calcium carbonate per tablet (n=31). Tablets in both groups had an identical

Table 1 Base-line characteristic values in the calcium group and vitamin D plus calcium group. Values for age, height, weight, BMI, mini mental score and baseline laboratory are given as mean±SD. None of the listed base-line characteristics showed significant differences between groups

Characteristics	Calcium group (*n*=31)	Vitamin D plus calcium group (*n*=33)	*P* value
Age (years)	85.7 (±5.9)	85.6 (±6.4)	NS
Height (cm)	155.8 (±7)	154.7 (±8.4)	NS
Weight (kg)	58.8 (±12.3)	58.9 (±14.2)	NS
BMI (kg/m2)	24.2 (±4.9)	24.5 (±4.6)	NS
Comorbidity score:			
0/1–2/>3 (%)	6/52/42	3/64/33	NS
Mini Mental Score	21.0 (±5.2)	20.8 (±5.2)	NS
Walking aid:			
no aid/cane/walker (%)	42/19/39	36/12/52	NS
Baseline laboratory:			
25–hydroxyvitamin D (ng/ml)	14.6 (±8.5)	16.7 (±9.6)	NS
iPTH (pg/ml)	36.3 (±17.2)	40.6 (±26.7)	NS
Baseline postural balance:			
roll angular displacement	1.03 (±0.74)	1.01 (±0.56)	NS
roll angular velocity	3.31 (±2.59)	2.99 (±2.40)	NS
pitch angular displacement	2.86 (±1.61)	2.15 (±1.38)	NS
pitch angular velocity	7.89 (±3.84)	7.25 (±5.42)	NS
Baseline dynamic balance:			
roll angular displacement	8.23 (±3.06)	7.95 (±3.19)	NS
roll angular velocity	28.54 (±9.65)	32.28 (±8.82)	NS
pitch angular displacement	42.54 (±10.10)	41.05 (±8.11)	NS
pitch angular velocity	143.26 (±41.64)	151.04 (±35.86)	NS

appearance, smell and taste and were administered twice daily with breakfast and dinner and swallowed in the presence of the study nurse to ensure compliance.

Patients, nurses and all investigators were blinded to the treatment assignment throughout the study. The treatment allocation was kept in sealed envelopes.

Patient descriptives

Comorbid conditions were evaluated by the Charlson Comorbidity Index [25]. Cognitive impairments were assessed by a Folstein Mini Mental Status (MMS) [26]. A dietician evaluated the mean calcium content of food consumed from each meal and drink during the baseline week. Overall diet was the same for all participants.

Balance assessment

Participants were asked in a standardized way to perform one postural task (postural balance: standing on two legs, eyes open, for 20 s) and one dynamic task (dynamic balance: get up from a standard height chair with arm rests, sit down and then stand up again and remain standing) at baseline and follow-up. For both postural and dynamic balance, four measures were assessed, including roll angular displacement, roll angular velocity, pitch angular displacement and pitch angular velocity. In the multivariate analysis the mean was taken from the two angular displacement measures and the two angular velocities.

Pitch (forward–backward) and roll (side–to–side) directions were measured with two angular velocity sensors attached to the hardened part of a motor–cycle–belt (SwayStar System of Balance International Innovations, Switzerland; http://www.b2i.info) [14]. The belt was placed around the subject so that the sensors were at the level of the lower back (lumbar spine level 2–3). The sensors were connected by a 10-m cable to a computer, which sampled the velocity signals every 100 ms and numerically integrated the velocity signals to yield angular displacement. The baseline drift of the sensors was maximally 36 degrees/h or 0.01 degrees/s. As our maximum task duration was 20 s, the maximum cumulative error of our measurements was maximally 0.2 degrees. The SwayStar balance method has been previously studied in different age groups of healthy subjects [15, 16], in institutionalized older persons [17], in patients recovering from an acute unilateral peripheral vestibular deficit [14], and in patients with chronic whiplash injury symptoms [18]. If compared with the Lord SwayMeter [19], which measures body sway while standing, the SwayStar allows balance assessment during dynamic tasks, such as getting in and out of a chair or walking. In addition, velocity of angular displacement is measured only by the SwayStar.

Postural and dynamic balance measures were validated by examining whether they predict eventual rate of falls. Specifically, we used postural and dynamic balance measures assessed at baseline, at 3–month follow-up and their change across time as predictors of the rate of falls within 3 months of treatment, controlling for treatment, age, BMI, Folstein MMS and baseline 25–hydroxyvitamin D serum concentrations.

Laboratory studies

Serum 25–hydroxyvitamin D and iPTH concentrations were measured by radio immunoassay (Nichols): intra-assay variation was 5.1% and 1.8%; inter-assay variation was 7.9% and 5.6%. All samples were frozen at –80°C and analyzed by the same person who was blinded to the treatment group in one batch.

Statistical analysis

All comparisons between treatment groups were based on an intention–to–treat analysis.

For group comparison at baseline we used two–sample *t*–tests, Wilcoxon rank sum tests, chi–square and Fisher's exact tests. We restricted this analysis to subjects with complete balance data in order to study the independent effect of change in balance on the rate of falls and whether the treatment effect on the rate of falls was attenuated by the change in balance.

The original analysis including all 122 subjects was powered on the rate of falls. Details are described elsewhere [7]. The adjusted analysis used the Poisson regression to compare the rate of falls in the two treatment groups in 64 subjects [20]. To address the issue of multiple falling and potential outliers, the response categories were collapsed to obtain more conservative results (0, 1, 2, 3, 4 , 5, >6 falls). One person in the calcium alone group fell 13 times, we therefore counted only six falls according to the highest fall category. Table 2 displays the number of falls by treatment. All analyses adjusted for age, BMI, Folstein MMS and baseline 25–hydroxyvitamin D levels. We did not adjust for length of follow-up as all 64 women completed the study.

In order to assess the validity of our method, baseline, 3–month follow-up and change in postural and dynamic balance was evaluated in all 64 participants as predictors of the rate of falls observed during the 3-month trial. This analysis was adjusted for treatment, age, BMI, MMS and baseline 25–hydroxyvitamin D. Once change in balance was added to the adjusted model, we evaluated whether balance attenuated the effect of treatment on the rate of falls comparing the effect size of treatment in regard to fall rate from the basic adjusted model and the balance adjusted model. Separate models were calculated for postural and dynamic balance.

A 5% significance level was maintained throughout these analyses, and all tests were two–sided. Data were analyzed by SAS computer program (version 8.2).

Results

Patient characteristics, laboratory measures and balance measures did not differ between groups at baseline (Table 1). Mean dietary calcium intake was low in all subjects, 600–700 mg per day. Vitamin D deficiency at study entry in the 64 subjects was highly prevalent by any definition (35–37): 42% of women had 25–hydroxyvitamin D serum concentrations below 12 ng/ml (30 nmol/l), 89% below 31 ng/ml (78 nmol/l) and 97% below 40 ng/ml (100 nmol/l).

Postural and dynamic balance assessment: validity

Table 2 displays the relative risk for the rate of falls (RR) by three different measures of postural and dynamic balance (baseline, follow-up and change over time). At all three time-frames, greater postural angular displacement and greater postural angular velocity significantly predicted an increased risk of falling, indicating that the balance method applied is valid.

For baseline postural balance, per unit increase in angular displacement the rate of falls increased by 56% (P=0.01), per unit increase in angular velocity the rate of falls increased by 11% (P=0.03). Similarly, for dynamic balance, per unit increase in angular displacement the rate of falls increased by 8% (P=0.04), per unit increase in angular velocity the rate of falls increased by 2% (P=0.07).

In general, the postural balance performance appeared to be a better predictor of the rate of falls than the dynamic measurement, which may be due to the frailty of our participants. We had to allow the use of the arm rests for the getting out of the chair test (dynamic balance).

Treatment effect of vitamin D and calcium on balance

The unadjusted mean change from baseline of postural and dynamic balance measures are depicted in Fig. 1a,b. For both postural and dynamic balance, the overall picture showed a deterioration of balance over time and was sug-

Table 2 Fall prediction by balance assessment at different time points (validation study). The RR of falling is shown for all 64 participants, as determined by the different measures of postural and dynamic balance, including baseline, follow-up and change over time. All analyses control for treatment, age, BMI, MMS and baseline 25–hydroxyvitamin D

Balance measure	RR (95% confidence interval) of falling by one unit change in balance measure		
	Baseline balance	Follow-up balance	Change in balance over time
Postural angular displacement	1.56 (1.10, 2.20)	1.55 (1.29, 1.87)	1.49 (1.21, 1.83)
Postural angular velocity	1.11 (1.01, 1.22)	1.08 (1.05, 1.13)	1.07 (1.03, 1.10)
Dynamic angular displacement	1.08 (1.01, 1.17)	1.04 (0.93, 1.17)	0.95 (0.89, 1.02)
Dynamic angular velocity	1.02 (1.00, 1.04)	1.03 (1.01, 1.05)	1.01 (0.99, 1.03)

gestive of a small benefit in the vitamin D plus calcium group over the calcium alone group, primarily for postural balance. However, none of the single measures reached statistical significance.

Both groups together showed a decrease in balance over time (paired *t*–tests; see legend to Fig. 1).

Falls

Of 37 falls in 64 women over a 12-week treatment period, nine (six persons) were in vitamin D plus calcium group and 21 (eight persons) in calcium alone group.

In the multivariate analysis, adjusting for age, bmi, MMS and baseline 25–hydroxyvitamin D, the rate of falls was 60% lower in the vitamin D plus calcium group (RR=0.40; 95% CI: 0.17, 0.94; Table 3).

If change in postural balance was added to the model that already adjusted for age, BMI, Folstein MMS and baseline 25–hydroxyvitamin D levels, there was some attenuation of the treatment effect [treatment RR after adjustment for angular displacement=0.62; 95% CI: 0.25, 1.59)/(treatment RR after adjustment for angular velocity=0.49; 95% CI: 0.20, 1.19)]; see Fig. 2. Similary, when change in dynamic balance was added to the model, there was some attenuation of the treatment effect; however, mostly in the velocity assessment [(treatment RR after adjustment for angular displacement=0.41; 95% CI: 0.17; 1.02)/(treatment RR after adjustment for angular velocity=0.54; 95% CI: 0.21, 1.44)].

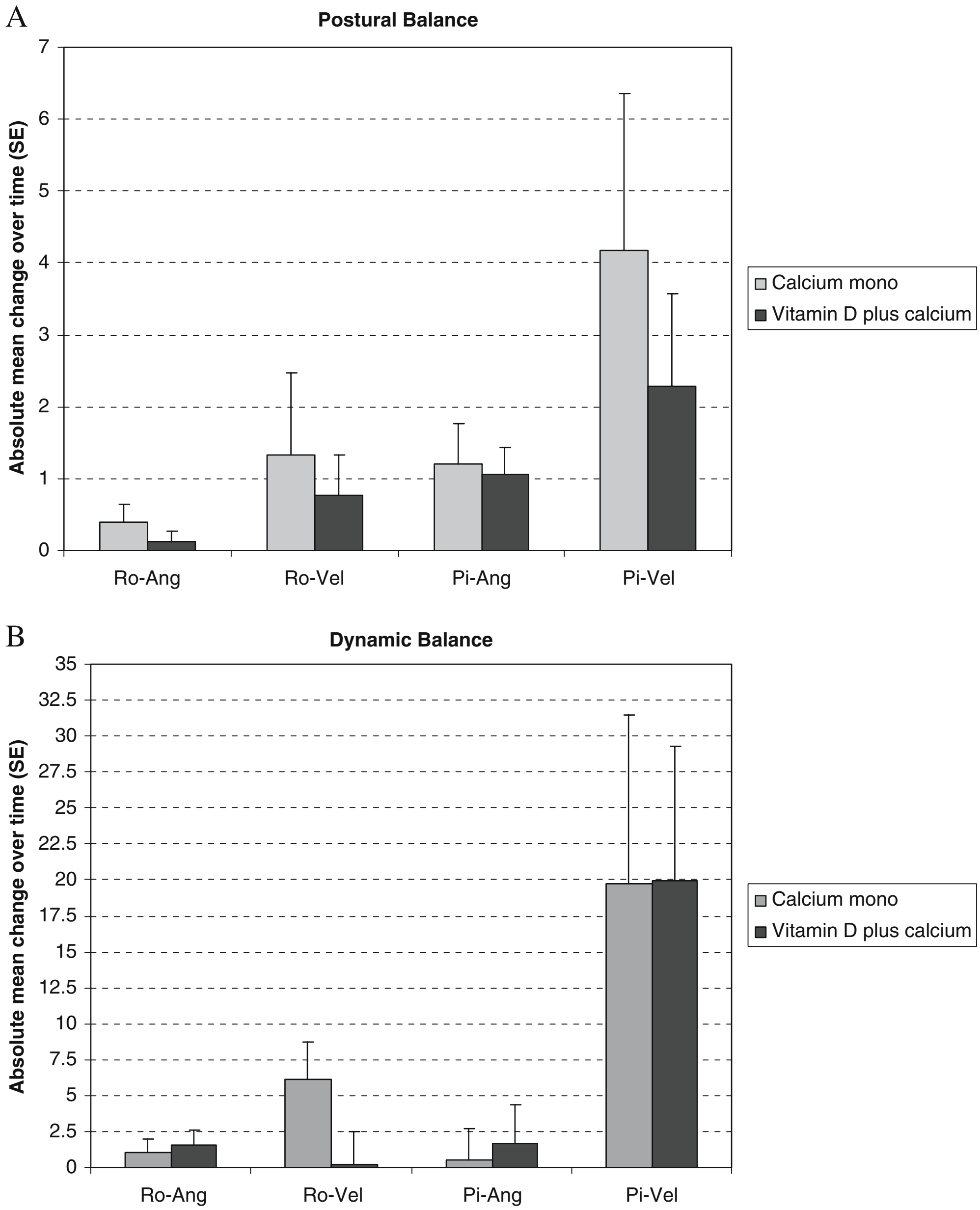

Fig. 1 Mean change from baseline in postural and dynamic balance measures by treatment. Postural and dynamic balance in general deteriorated over time with an increase in trunk angle and velocity measures. The mean change over time of trunk angle and velocity measures are shown. *Error bars* represent the standard error of the mean change (SE). *Ro-ang* roll angular displacement, *Ro-vel* roll angular velocity, *Pi-ang* pitch angular displacement, *Pi-vel* pitch angular velocity. *Postural balance:* for all postural balance measures, there was a suggestion of a benefit of vitamin D plus calcium compared with calcium alone, however without reaching statistical significance. For both treatment groups together (n=64), three out of four postural balance measures increased significantly over time (*P* values for paired *t*–test: Ro-ang=0.06; Pi-ang=0.002; Ro-vel<0.0001; Pi-vel=0.01). *Dynamic balance:* only for the roll velocity measure, there was a suggestion of a benefit of vitamin D plus calcium compared with calcium alone, without reaching statistical significance. For both treatment groups together, three out of four dynamic balance measures increased over time, one reaching significance and two approaching significance (*P* values for paired *t*–test: Ro-ang=0.07; Pi-ang=0.54; Ro-vel=0.06; Pi-vel=0.01)

Table 3 Absolute distribution of falls. Vitamin D reduced the rate of falls by 60% (OR=0.40; 95% CI: 0.17, 0.94) controlling for age, BMI, MMS and baseline 25–hydroxyvitamin D

Number of falls	Number of subjects receiving the treatment	
	Vitamin D plus calcium group	Calcium alone group
0	27	23
1	5	4
2	0	1
3	0	0
4	1	1
5	0	1
≥6	0	1
Total	9	21

Biochemical changes

Among subjects in the vitamin D plus calcium group, there was a significant increase in serum 25–hydroxyvitamin D (+8.1 ng/ml) if compared with the calcium alone group (–1.4 ng/ml; P<0.001). In regard to intact PTH, there was a significant difference between groups with a larger decrease in the vitamin D plus calcium group (–19.2 pg/ml) compared with the calcium alone group (–6.2 pg/ml; P=0.035).

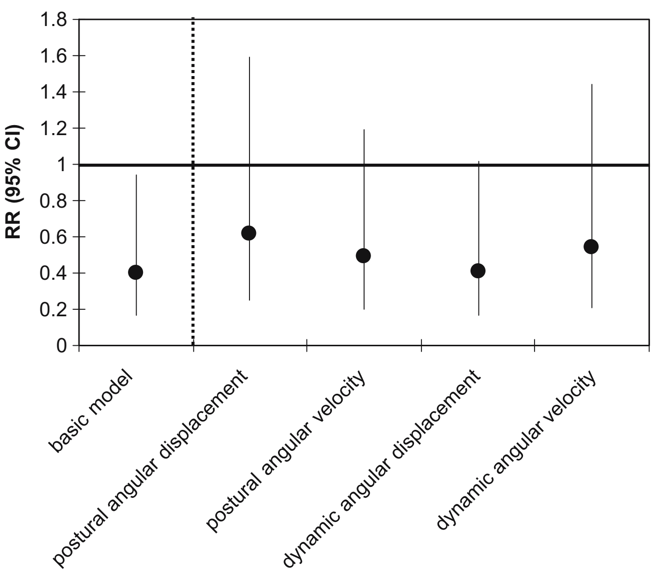

Fig. 2 Is the treatment effect on falls mediated by effects on postural or dynamic balance? The RR of falling (*dot*), comparing vitamin D plus calcium with calcium alone with the 95% confidence interval (*vertical line*) based on several regression models. To the left of the dotted vertical line, the basic model is displayed controlling for age, BMI, baseline 25–hydroxyvitamin D levels and MMS (RR=0.40; 95% CI: 0.17, 0.94). To the right of the *dotted line*, additional adjustments for balance measures were performed to discern whether the treatment effect on falls was attenuated by a change in balance control

Discussion

In this study, we first established the validity of a new quantitative balance assessment method in regard to fall risk prediction. Both postural (standing on two legs, eyes open, for 20 s) and dynamic balance (get up from a standard height chair with arm rests, sit down and then stand up again and remain standing) were significant predictors of the rate of falls occurring in frail elderly women over a 3-month follow-up. This association was independent of treatment, age, BMI, Folstein MMS and baseline 25–hydroxyvitamin D serum concentrations.

Once the validity of our method was established, we evaluated whether the observed treatment effect of vitamin D plus calcium on falls was mediated by a change in postural or dynamic balance. Similar to the total sample in the original RCT, this sub-sample of elderly women with complete balance assessment had a statistically significant 60% reduction in the rate of falls given vitamin D plus calcium supplementation compared with calcium alone [7]. By adding change in balance over time to the model and assessing the thereby introduced attenuation of the treatment effect, we documented that balance is a mediator of the treatment effect of vitamin D on falls. Up to 22% of the treatment effect could be explained by a change in postural balance, while up to 14% were explained by a change in dynamic balance.

Our observation that the anti-fall effect of vitamin D is in part mediated by a change in balance is supported by previous observations. First, impaired balance is an established risk factor for falls in older persons [21, 22], as confirmed in our study. Furthermore, a significant direct benefit of vitamin D plus calcium on postural body sway was previously documented in the study by Pfeifer and co-workers, where 800 IU vitamin D plus 1,200 mg calcium per day compared with 1,200 mg calcium alone, improved body sway (standing on two legs for 30 s with eyes open) by 9% over 2 months (P value for group comparison=0.044) [10]. In our study, we observed a possible direct benefit of vitamin D plus calcium on most postural balance measures and one dynamic measure, although none of the single measures reached significance. We may have missed significance due to the smaller sample size with greater variation in our study (Pfeifer and co-workers: n=148; our study: n=64). In addition, there were differences in the type of dwelling (the trial by Pfeifer and co-workers studied ambulatory elderly women and we included very frail elderly women), age (mean age 74 years vs mean age 85 in our trial), and baseline 25-hydroxyvitamin D levels (26 nmol/l vs 41 nmol/l in our trial) between the studies. Moreover, in the trial by Pfeifer and colleagues, no information was provided on whether balance control mediated the treatment effect of vitamin D on fall prevention [10]. The authors collected information on falls as a secondary outcome during a 1-year uncontrolled follow-up and documented a significant reduction in the number of falls among women who had received vitamin D plus calcium in the first 2 months of their study. Also, the authors did not provide data on whether balance predicted the risk of falling in their study. Furthermore, Pfeifer and co-workers used the SwayMeter [19], which is a somewhat simpler method restricted to body sway assessment while standing. As a direct comparison between the methods is missing, it is unclear which method is superior. One important advantage of the SwayStar, however, is the possibility of measuring balance during dynamic tasks, as well as angle velocities.

The magnitude of the treatment effect of vitamin D plus calcium mediated through a change in balance was 22% for postural balance and 14% for dynamic balance. Thus, additional mediators of the treatment effect of vitamin D plus calcium must be present to explain the 60% reduction in the rate of falling. Apart from possible unknown factors, previous studies indicate that vitamin D is associated with greater muscle strength [7, 9, 23] and better lower extremity function [11, 23–26].

The mechanism how vitamin D may improve muscle strength and function, as well as balance due to improved strength, is that 1,25–dihydroxyvitamin D, the active vitamin D metabolite, binds to a vitamin-D-specific nuclear receptor in muscle tissue [27–29], leading to de novo protein synthesis [6, 26] and muscle cell growth [26]. Six lines of evidence support this hypothesis. (1) Proximal muscle weakness is a prominent feature of the clinical syndrome of vitamin D deficiency [6, 9] and may be present even before bone alterations develop [9]. (2) Highly specific receptors for 1,25–dihydroxyvitamin D are expressed in human muscle tissue [6, 26], decline with age [8], and promote protein synthesis in the presence of 1,25–dihydroxyvitamin D [26, 30]. (3) A vitamin D receptor (VDR)–dependent action of vitamin D on muscle is supported by findings in *VDR*-gene-deleted mice ($VDR^{-/-}$), where the absence of the VDR causes muscle abnormalities independent of secondary systemic metabolic changes [29]. (4) The *VDR* genotype is associated with quadriceps and grip strength in non-obese elderly women [31]. (5) Several observational studies point towards a positive association between 25-hydroxyvitamin D [11, 24, 32] or 1,25–dihydroxyvitamin D levels [23] and muscle strength or lower extremity function in older persons. In a large US national survey of ambulatory persons aged 60 or older 25-hydroxyvitamin D levels were significantly associated with lower extremity function independent of gender and activity level [11]. Finally, fall prevention efficacy by vitamin D has been shown in a recent meta-analysis of RCTs performed by some of the authors [5].

A strength of the study is its double-blind and randomized-controlled design and the demonstrated validity of the balance method applied. Furthermore, in addition to the protection provided by randomization, we were able to adjust for important confounders, including age, BMI, Folstein MMS and baseline 25–hydroxyvitamin D levels.

There are several limitations to our study. First, this is a secondary data analysis of the original RCT limited to a sub-sample of participants with complete balance assessment. Thus the significant treatment effect may be questioned given the smaller number of participants in this sub-sample with complete balance assessment. However, the magnitude of the treatment effect of vitamin D plus calcium observed in this sub-sample (60% fall reduction) is within the 95% CI of the original trial [49% (14–71%)] [7]. Furthermore, our sub-sample did not differ in important baseline characteristics from the rest of the original study population, suggesting that our results are generalizable to the total study sample. However, generalizability may be limited to institutionalized elderly women with low vitamin D serum concentrations.

In summary, in this double-blind RCT, postural and dynamic balance control were important independent predictors of the risk of falling in frail elderly women and mediated up to 22% of the anti-fall effect of vitamin D plus calcium. Thus, change in balance is an important target in fall prevention with vitamin D. Furthermore, the proposed method in balance assessment, especially trunk sway angular displacement in postural balance control, may be useful in future trials and cohort studies where falls are evaluated in older individuals.

Acknowledgements The authors are indebted to John Orav (Department of Biostatistics, Harvard School of Public Health, Boston, USA) for his statistical advice and to Stephen M. Ferrari (independent) for his insights and assistance in the preparation of this manuscript. We are grateful to the nurses of the Geriatric Departments for their great commitment in recording the falls of our patients. This study was supported by the following: the International Foundation for the Promotion of Nutrition Research and Nutrition Education (ISFE), the Swiss Orthopedic Society, the Swiss Foundation for Nutrition Research (SFEFS), and Strathmann AG, Germany.

References

1. Tinetti ME, Williams CS (1998) The effect of falls and fall injuries on functioning in community-dwelling older persons. J Gerontol A Biol Sci Med Sci 53(2):M112–119
2. Tinetti ME, Williams CS (1997) Falls, injuries due to falls, and the risk of admission to a nursing home. N Engl J Med 337 (18):1279–1284
3. Tinetti ME, Speechley M, Ginter SF (1988) Risk factors for falls among elderly persons living in the community. N Engl J Med 319(26):1701–1707
4. Sattin RW, Lambert Huber DA, DeVito CA et al (1990) The incidence of fall injury events among the elderly in a defined population. Am J Epidemiol 131(6):1028–1037
5. Bischoff–Ferrari HA, Dawson–Hughes B, Willett CW et al (2004) Effect of vitamin D on falls: a meta-analysis. JAMA 291 (16):1999–2006
6. Boland R (1986) Role of vitamin D in skeletal muscle function. Endocr Rev 7:434–447
7. Bischoff HA, Stahelin HB, Dick W et al. (2003) Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. J Bone Miner Res 18(2):343–351
8. Bischoff–Ferrari HA, Borchers M, Gudat F, Durmuller U, Stahelin HB, Dick W (2004) Vitamin D receptor expression in human muscle tissue decreases with age. J Bone Miner Res 19 (2):265–269
9. Glerup H, Mikkelsen K, Poulsen L et al. (2000) Hypovitaminosis D myopathy without biochemical signs of osteomalacic bone involvement. Calcif Tissue Int 66(6):419–424

10. Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C (2000) Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. J Bone Miner Res 15(6):1113–1118
11. Bischoff–Ferrari HA, Dietrich T, Orav EJ et al. (2004) Higher 25–hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > or =60 y. Am J Clin Nutr 80(3):752–758
12. Nevitt MC, Cummings SR, Kidd S, Black D (1989) Risk factors for recurrent nonsyncopal falls. A prospective study. Jama 261(18):2663–2668
13. Buchner DM, Hornbrook MC, Kutner NG et al. (1993) Development of the common data base for the FICSIT trials. J Am Geriatr Soc 41(3):297–308
14. Allum JH, Adkin AL (2003) Improvements in trunk sway observed for stance and gait tasks during recovery from an acute unilateral peripheral vestibular deficit. Audiol Neurootol 8(5):286–302
15. Allum JH, Zamani F, Adkin AL, Ernst A (2002) Differences between trunk sway characteristics on a foam support surface and on the Equitest ankle–sway–referenced support surface. Gait Posture 16(3):264–270
16. Gill J, Allum JH, Carpenter MG et al. (2001) Trunk sway measures of postural stability during clinical balance tests: effects of age. J Gerontol A Biol Sci Med Sci 56(7):M438–447
17. de Hoon EW, Allum JH, Carpenter MG et al. (2003) Quantitative assessment of the stops walking while talking test in the elderly. Arch Phys Med Rehabil 84(6):838–842
18. Sjostrom H, Allum JH, Carpenter MG, Adkin AL, Honegger F, Ettlin T (2003) Trunk sway measures of postural stability during clinical balance tests in patients with chronic whiplash injury symptoms. Spine 28(15):1725–1734
19. Lord SR, Clark RD, Webster IW (1991) Postural stability and associated physiological factors in a population of aged persons. J Gerontol 46(3):M69–76
20. Rosner B (2000) Fundamentals of Biostatistics, 5th edn, pp 98–105
21. Campbell AJ, Reinken J, Allan BC, Martinez GS (1981) Falls in old age: a study of frequency and related clinical factors. Age Ageing 10(4):264–270
22. Wu G (2002) Evaluation of the effectiveness of Tai Chi for improving balance and preventing falls in the older population —a review. J Am Geriatr Soc 50(4):746–754
23. Bischoff HA, Stahelin HB, Urscheler N et al. (1999) Muscle strength in the elderly: its relation to vitamin D metabolites. Arch Phys Med Rehabil 80(1):54–58
24. Mowe M, Haug E, Bohmer T (1999) Low serum calcidiol concentration in older adults with reduced muscular function. J Am Geriatr Soc 47(2):220–226
25. Gloth FM 3rd, Smith CE, Hollis BW, Tobin JD (1995) Functional improvement with vitamin D replenishment in a cohort of frail, vitamin D–deficient older people. J Am Geriatr Soc 43(11):1269–1271
26. Sorensen OH, Lund B, Saltin B et al. (1979) Myopathy in bone loss of ageing: improvement by treatment with 1 alpha–hydroxycholecalciferol and calcium. Clin Sci (Colch) 56(2):157–161
27. Simpson RU, Thomas GA, Arnold AJ (1985) Identification of 1,25–dihydroxyvitamin D3 receptors and activities in muscle. J Biol Chem 260(15):8882–8891
28. Bischoff HA, Borchers M, Gudat F et al. (2001) In situ detection of 1,25–dihydroxyvitamin D3 receptor in human skeletal muscle tissue. Histochem J 33(1):19–24
29. Endo I, Inoue D, Mitsui T et al. (2003) Deletion of vitamin D receptor gene in mice results in abnormal skeletal muscle development with deregulated expression of myoregulatory transcription factors. Endocrinology 144(12):5138–5144 13
30. Haddad JG, Walgate J, Min C, Hahn TJ (1976) Vitamin D metabolite-binding proteins in human tissue. Biochim Biophys Acta 444(3):921–925
31. Geusens P, Vandevyver C, Vanhoof J, Cassiman JJ, Boonen S, Raus J (1997) Quadriceps and grip strength are related to vitamin D receptor genotype in elderly nonobese women. J Bone Miner Res 12:2082–2088
32. Dhesi JK, Bearne LM, Moniz C et al. (2002) Neuromuscular and psychomotor function in elderly subjects who fall and the relationship with vitamin D status. J Bone Miner Res 17(5): 891–897